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PREDNISOLONE IN TREATMENT OF PULMONARY TUBERCULOSIS: A CONTROLLED TRIAL

FINAL REPORT TO THE RESEARCH COMMITTEE OF THE TUBERCULOSIS SOCIETY OF SCOTLAND*

BY

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The Research Committee of the Tuberculosis Society of Scotland (1957) published a preliminary account of the results of a controlled trial of the use of prednisolone in the treatment of pulmonary tuberculosis. That report was an analysis of the results attained in 110 patients who had completed six months' treatment. This present report is concerned with the results achieved in all patients—213 in number—admitted to the trial between February, 1956, and December, 1957. The patients were studied for a period of 12 months from the beginning of treatment.

The physicians participating in the trial were:—Aberdeen: Drs. Douglas Bell and Robert Fraser. Bangour: Drs. G. J. Summers, K. Murray, G. G. Robertson, and J. H. R. Ramsay. Dundee: Drs. D. H. Smith, R. N. Johnston, W. Lockhart, and R. T. Ritchie. East Fortune: Drs. W. A. Murray, A. P. Littlewood, and Rose Donaldson. Edinburgh: Professor J. W. Crofton, Drs. I. W. B. Grant, N. W. Horne, H. M. MacLeod, A. Pines, J. D. Ross, the late J. McD. Simpson, A. R. Somner, and J. Williamson. Glasgow: Drs. W. M. Borthwick, G. B. Marshall Clarke, J. E. Geddes, G. Johnson, Helen S. Kennedy, R. S. Kennedy, J. S. Marshall, and W. G. Wimsett. Lochmaben: Drs. C. Clayson, J. A. Cameron, J. B. Cochran, and B. R. Hillis.

The trial was co-ordinated by Dr. D. T. Kay, Royal Victoria Hospital Tuberculosis Trust Research Fellow.

Plan of Investigation

Cases for admission to the trial were selected by physicians at the seven centres, provided that such cases conformed to certain previously defined criteria. The criteria were as follows: (1) It should be expected that the patient would co-operate to the extent of remaining in hospital for six months. (2) No surgical treatment or collapse therapy should be envisaged for six months from the beginning of treatment. (3) Patients would not be suitable for admission to the trial under the following circumstances: (*a*) if they had received collapse therapy at any time; (*b*) if chemotherapy had been given previously (the protocol allowed patients to be admitted to the trial who had been started on chemotherapy less than a month prior to acceptance: this was applicable to four cases only, all the remaining patients beginning chemotherapy on the date of entry to the trial); (*c*) if they had tubercle bacilli known to be resistant to streptomycin, *para*-aminosalicylic acid (P.A.S.), or isoniazid; (*d*) if they were less than 15 years of age; (*e*) if active extrapulmonary disease was present; (*f*) if they were pregnant or within three months of parturition; (*g*) if they suffered from any condition—for example, peptic ulcer, hypertension, cardiac failure, etc.—known to be adversely affected by corticosteroid therapy.

The patient was allocated by the physician to one of three subgroups: (1) *Acute*: where the disease was judged on clinical and radiological grounds to have been present less than two years. (2) *Chronic*: where the disease was judged on clinical and radiological grounds to have been present for more than two years. (3) *Chronic disease with acute spread.*

The physician, being satisfied that the necessary criteria were observed and having allocated the patient to one of the subgroups of disease type, submitted the name of the patient to the co-ordinator. The patient was allocated centrally to one of two treatment groups from prearranged lists based upon random sampling numbers, the physician in charge of the case thus being entirely unaware of the likelihood of allocation to any specific group.

Treatment Groups

Control Group (Chemotherapy Only).—It was agreed to treat all cases according to the following plan of chemotherapy for the first six months. In order to minimize the toxic effects of streptomycin on the eighth cranial nerve, two categories were designated as follows: (i) Patients aged 40 years or under: streptomycin sulphate (or mixtures of streptomycin and dihydrostreptomycin) 1 g. daily, isoniazid 100 mg. twice daily. (ii) Patients over 40 years: streptomycin sulphate (or mixtures of streptomycin and dihydrostreptomycin) 1 g. thrice weekly, sodium P.A.S. 5 g. twice daily, isoniazid 100 mg. twice daily.

Prednisolone Group (Chemotherapy plus Prednisolone).—(i) Chemotherapy as in control group. (ii) Prednisolone,† 5 mg. four times daily for three

*The members of the Research Committee of the Tuberculosis Society of Scotland were Dr. Christopher Clayson (chairman), Dr. W. M. Borthwick, Dr. L. G. Bruce, Professor J. W. Crofton, Dr. J. Cuthbert, Dr. Agnes R. Macgregor, Dr. W. A. Murray, Dr. G. J. Summers, and Dr. N. W. Horne (secretary, City Hospital, Edinburgh).

†Prednisolone was administered in the form of "deltacortril."

months, plus A.C.T.H. gel 30 units I.M. on two successive days every fortnight during prednisolone therapy. (iii) Potassium citrate 2 g. twice daily during prednisolone therapy.

In both groups, patients were required to remain on bed rest for three months and to remain in hospital for six months. All patients, with the exception of four in whom treatment was stopped in the twelfth month, received treatment for a minimum of 12 months.

The following observations were recorded prior to the beginning of treatment and at monthly intervals for the first six months of the trial and at the ninth and twelfth months: (1) General condition. (2) Weight. (3) Radiograph of chest. (4) Erythrocyte sedimentation rate (E.S.R.). (5) Sputum or gastric lavage or laryngeal swabs for culture and sensitivity tests to streptomycin, P.A.S., and isoniazid. (6) Blood-pressure. (7) Urine for albumin and sugar. (8) Serum electrolytes (sodium, potassium, and chlorides). The latter three investigations were omitted at the ninth and twelfth months.

Withdrawals from Analysis

It was found necessary to withdraw 35 cases from analysis—18 in the control group and 17 in the prednisolone group—for reasons shown in Table I.

TABLE I.—*Withdrawals from Analysis*

	Control (109 Cases)	Prednisolone (104 Cases)
Primary drug resistance	2	4
Extrapulmonary tuberculosis	2	0
Coexisting tumour	0	2
Non-tuberculous	0	1
Pregnancy	0	1
Patients leaving hospital against advice	7	9
Incomplete data	4	0
Default of protocol	3	0
	18	17

Thus 178 cases remain for analysis—91 in the control group and 87 in the prednisolone group.

Composition and Comparability of Groups

The two treatment groups have been compared according to age and sex; type of disease; extent of disease—unilateral or bilateral, and number of zones involved; existence of cavitation; and presence of tubercle bacilli on culture of pulmonary secretions at the start of treatment. Details are shown in Table II. It will be seen that the two groups are highly comparable in all respects.

TABLE II.—*Composition and Comparability of Groups*

	Control (91 Cases)	Prednisolone (87 Cases)
Age in years (average)	33·0	31·0
Sex: Male	63·7%	57·5%
Sex: Female	36·3%	42·5%
Type of disease: Acute	84·6%	88·5%
Type of disease: Chronic	1·1%	0·0%
Type of disease: ,, plus acute	14·3%	11·5%
Extent of disease: No. of zones (Av.)	3·7	3·8
Extent of disease: Unilateral	28·6%	28·8%
Extent of disease: Bilateral	71·4%	71·2%
Cavitated disease	65·9%	65·5%
Sputum positive (culture)	87·9%	85·0%

Attention is also drawn to the fact that more than four-fifths of the patients were sputum-positive, 65% showed cavitation clearly demonstrable on a postero-anterior radiograph, and the average extent of disease in the investigation was almost four zones. Under the classification of the National Tuberculosis Association of the United States of America, 48% of the cases had far-advanced disease, 47% moderately advanced disease, and 5% minimal disease.

Results

General Condition and Weight Gains.—In general, the clinical state of the patients in the prednisolone group improved more rapidly than those in the control group. The amount of average weight gain is shown in Fig. 1. It will be seen that patients in the prednisolone

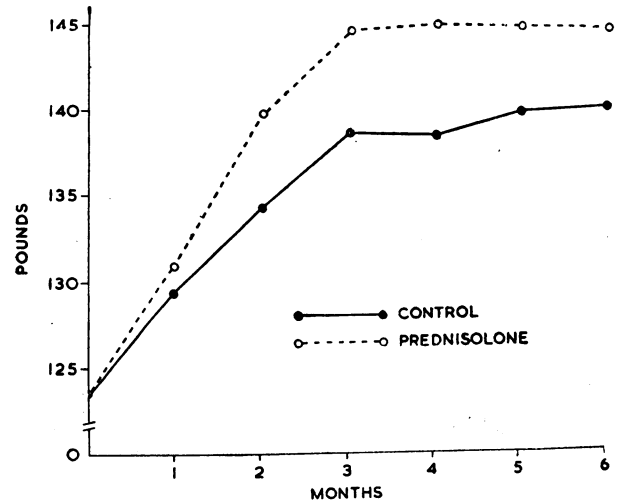

FIG. 1.—Analysis of average weight gain.

group gained weight more rapidly than those in the control group, though the difference is not statistically significant. The weight of patients in the prednisolone group seemed to become stabilized after three months, whereas patients in the control group continued to gain weight up to six months. The fact that there was no loss of weight in the former group when prednisolone was stopped suggests that the more rapid gain in weight was not due to fluid retention of any significant degree. The analysis of weight gain was not carried beyond six months because of the numerous variables which obtained subsequent to this period.

Erythrocyte Sedimentation Rate.—The average E.S.R. showed a rapid fall to within normal limits in the first month of treatment in the prednisolone group (Fig. 2) compared with the more leisurely fall in the control group, in which the normal range was not reached until the fourth month. A slight rise in E.S.R. occurred in the prednisolone group on withdrawal of the steroid

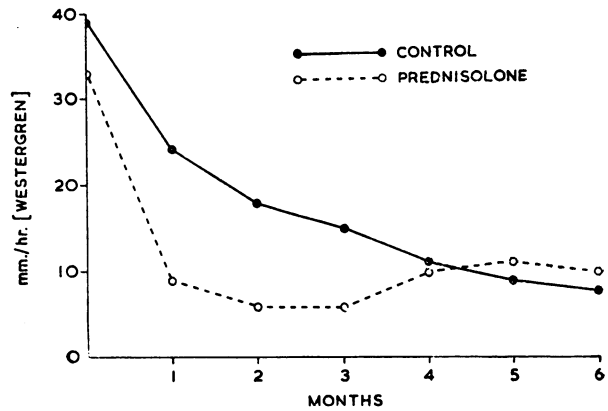

FIG. 2.—Analysis of average E.S.R.

TABLE III.—*Analysis of Radiographic Changes**

Month of Treatment:	1		2		3		4		5		6		9†		12†	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Improvement:																
Considerable ..	0·0	3·5	2·2	16·0	11·0	26·4	17·6	29·1	27·5	35·7	36·6	48·2	46·3	60·2	57·0	70·3
Moderate	12·2	33·8	27·5	44·7	40·7	51·8	46·1	45·4	41·1	44·7	45·6	34·5	38·7	30·8	34·2	20·3
Slight	61·1	54·5	61·5	33·5	41·7	18·4	34·1	18·5	25·3	17·2	15·6	13·8	12·5	7·7	6·4	8·1
No change	26·7	8·2	8·8	5·7	5·5	3·4	2·2	3·5	1·1	1·2	2·2	1·2	2·5	1·3	2·5	1·3
Deterioration ..	0·0	0·0	0·0	0·0	1·1	0·0	0·0	3·5	0·0	1·2	0·0	2·4	0·0	0·0	0·0	0·0

* In comparison with pretreatment radiograph. † Excluding patients treated by surgical measures. C = Control. P = Prednisolone.

therapy after three months. The fall in the E.S.R. in the first month is statistically significant ($P<0.01$) in favour of the prednisolone group.

Radiographic Changes.—All radiographs were assessed by a panel experienced in the reading of radiographs of the chest. The observers were unaware of the treatment group to which the radiographs belonged. Each series of radiographs was assessed on two separate occasions. The radiographs were recorded as showing improvement, no change, or deterioration. The degree of improvement—or deterioration—was recorded as slight, moderate, or considerable. (The degree of change is shown in comparison with the radiographic appearances at the beginning of treatment.) The results of the analysis of radiographic change are shown in Table III.

The trend of radiographic improvement throughout the first six months proved to be in favour of the prednisolone group to a statistically significant degree. The proportion of cases showing considerable and moderate improvement at each month was statistically highly significant ($P<0.01$) at the first, second, and third months, and significant ($P<0.05$) at the fourth month. Thereafter, although the percentage of cases in the prednisolone group showing considerable improvement remained higher throughout the remaining months, this was not statistically significant. These results are in accord with those recorded in the preliminary report, apart from the fact that improvement of a highly significant degree was shown only in the second month in the preliminary analysis.

In three cases in the prednisolone group and one in the control group, radiographic deterioration as compared with the initial radiograph was observed. The deterioration was in each case only temporary. All subsequently showed improvement, even although no change was made in treatment.

The cumulative analysis shown in Table III, however, fails to demonstrate a phenomenon which occurred in a proportion of the prednisolone group between the third and fourth months of treatment—that is, immediately subsequent to the withdrawal of prednisolone. Radiographic deterioration occurred between the third and fourth months in eight patients (11%). No similar deterioration was observed in the control group at this period. As previously indicated, radiographic deterioration, when it occurred, was temporary.

In all patients an attempt was made to express the residual opacity present in the film taken at 12 months as a percentage of the extent of opacity present before treatment. The average residual opacity in the prednisolone group was 18% of the original and in the control group 24%. When the amount of residual opacity was compared in patients with more extensive disease—that is, four, five, or six zones—the average residual opacity was 16% of the original in the prednisolone group and 23.3% in the control group. Although the amount of residual opacity was less in the prednisolone group, both in the group as a whole and in the far-advanced patients within the group, the difference is not statistically significant. Theoretically, prednisolone may suppress the formation of fibrous tissue. An analysis of the amount of "fibrotic" opacity at the end of treatment in comparison with that present before treatment showed, however, no difference beween the two groups.

Cavity Closure.—The total number of cases showing cavitation was 117, of which 60 occurred in the control and 57 in the prednisolone group. The trend of cavity closure is shown in Table IV. It will be seen that there is no significant difference in the rate of cavity closure between the two groups. At the end of six months the percentage of cavity closure was 73 in the control and 70 in the prednisolone group. Between the seventh and twelfth months, 10 patients in the control group and 11 patients in the prednisolone group were treated by surgery. The figures for cavity closure had risen to 90 and 87% respectively at the end of 12 months in those patients treated by drug therapy alone.

TABLE IV.—*Analysis of Cavity Closure*

Months	Cavity Closure (%)	
	Control	Prednisolone
1	13	16
2	27	32
3	45	45
4	58	51
5	67	54
6	73	70
9	(82)*	(81)*
12	(90)*	(87)*

* Ten patients in the control group and 11 in the prednisolone group underwent surgical measures between the seventh and twelfth months. The percentages refer to the remainder.

Sputum Conversion.—The rate of sputum conversion is shown in Table V. The rate in the prednisolone group was higher throughout the first four months. By the end of the sixth month all but one of the 178 cases in the trial had become negative on culture, the exception being one case in the prednisolone group. One further case in this group had an isolated positive culture between the sixth and ninth months. Both cases were treated subsequently by resection. No instance of the

TABLE V.—*Analysis of Sputum Conversion (Negative Culture)*

Months	Control (%)	Prednisolone (%)
1	31	46
2	49	73
3	68	77
4	82	86
5	90	92
6	100	99
9	(100)*	(97)*
12	(100)*	(100)*

* Ten patients in the control group and 11 in the prednisolone group underwent surgical measures between the seventh and twelfth months. The percentages refer to the remainder.

development of drug resistance was recorded. The rate of sputum conversion was more rapid in the prednisolone group to a statistically significant degree ($P<0.01$) in the second month only.

Surgical Treatment and Collapse Therapy.—Surgical treatment or collapse therapy was performed between the seventh and twelfth months in 21 patients—10 in the control group and 11 in the prednisolone group. Two patients in each group were treated by pneumoperitoneum. In the control group eight patients were treated by major surgery (three thoracoplasties and five resections), and in the prednisolone group ten patients were treated surgically (three thoracoplasties and seven resections). One post-operative death occurred from pulmonary embolism on the seventeenth post-operative day. This patient was in the prednisolone group.

Deaths.—One death occurred in each group. One patient in the control group died from polyarteritis nodosa in the twelfth month of treatment, and, as recorded above, one patient in the prednisolone group died post-operatively of pulmonary embolism.

Toxic Effects

Chemotherapy.—Evidence of vestibular disturbance was recorded in five (two in the streptomycin thrice-weekly category) of the 91 patients in the control group, and in two out of the 87 in the prednisolone group. Hypersensitivity in the form of fever and rash was observed in four cases (two to streptomycin, two to streptomycin and P.A.S.) in the control group, and in five (two to streptomycin and three to P.A.S.) in the prednisolone group. In three of the patients in the latter group the hypersensitivity reaction was reported in the eighth month of treatment. In one patient hypersensitivity was so severe that desensitization was impossible. Transient rashes occurred within seven days of the withdrawal of prednisolone in 17 patients (19.5%). The rash was recorded mainly as an erythematous reaction, though it was sometimes papular. The face and trunk were especially involved and the rash was itchy and often scaled. The condition subsided without interruption of treatment.

Prednisolone Therapy.—Cessation of prednisolone therapy on account of serious toxic effects was necessary in only two cases (2.3%). In one case glycosuria was observed and a diabetic curve revealed in the first month of treatment. One patient showed a marked rise in diastolic blood-pressure to 140 mm. in the sixth week of treatment. In both instances prednisolone therapy was immediately stopped and evidence of toxicity rapidly disappeared. Both cases are included in the analysis. Minor side-effects were also recorded. Marked *obesity* was observed in three patients and *mooning* of the face in 18 (21%) patients (11 females and 7 males). *Hirsutism* was reported in one case. Hypertension to the degree of persistent elevation of the diastolic pressure above 100 mm. in patients whose diastolic pressure was previously within the normal limits occurred in 11 (13%) (2 females and 9 males) apart from the patient mentioned above whose prednisolone was stopped on this account. The elevation was transient in all cases, and no permanent ill effects were recorded in any of them. *Transient glycosuria* was observed in six patients (7%). Reference has already been made to one patient showing marked glycosuria associated with a diabetic curve. No significant disturbance of *serum electrolytes* was observed.

Discussion

There was some evidence to suggest that corticosteroid therapy is effective in certain tuberculous conditions—where highly specialized tissues are involved, such as the meninges or the eye, when hypersensitivity to antituberculous drugs occurs, when there is a large effusion in the pleural or peritoneal cavity, and, of course, as replacement therapy where adrenal destruction is due to tuberculosis. When this trial was begun, the evidence in relation to the value of corticosteroid drugs in pulmonary tuberculosis was equivocal and controversial, though the early work of Cochran (1954) and Houghton (1954) was encouraging. The evidence is admirably reviewed by Johnson and Davey (1954).

This investigation was designed to assess whether corticosteroid therapy could hasten improvement in pulmonary tuberculosis treated by chemotherapy. It was also important to know whether corticosteroid therapy was ever responsible for deterioration in the tuberculous condition and whether the known hazards of corticosteroid therapy outweighed any advantages which might accrue.

The anti-inflammatory action of the corticosteroids seems to be responsible for the more rapid reduction of the toxic effects caused by tuberculous infection. This phenomenon has been described by Houghton (1954) and others, and was confirmed in this investigation. In general, the patients receiving prednisolone made quicker subjective improvement. Weight gain was more rapid also, though the difference between the groups was not statistically significant. The anti-inflammatory effect was also shown by the rate of fall in the E.S.R. which was statistically in favour of the prednisolone group at the end of the first month. The E.S.R. had in fact reached, on average, a normal level by this time.

The trend of radiographic improvement was statistically significant throughout the first six months, and was still much in favour of the prednisolone group at nine months and at the end of a year. Whereas in the preliminary report it appeared that the difference in any one month was of highly significant degree only in the second month, further analysis of the whole series demonstrates a high degree of significance in favour of the prednisolone group in the first, second, and third months, and a significant difference at a 1 in 20 level in the fourth month. An attempt was also made—and the inaccuracies in such an attempt are not underestimated—to assess the extent of the residual opacity at 12 months as compared with the extent of opacity at the beginning of treatment. Again the prednisolone group fared better than the group treated with chemotherapy, though the difference was not statistically significant.

Despite increasing recognition of the fact that open-cavity healing is compatible with a highly satisfactory prognosis (Douglas and Horne, 1956), cavity closure is still used as an important criterion of progress. Cavity closure at the end of six months was 73% in the control group and 70% in the prednisolone group, there being no significant difference in the rate of closure between the groups. A similar proportion subsequently underwent surgical treatment in the two groups, and when these were excluded cavity closure had risen to 90 and 87% respectively at the end of 12 months.

The rate of sputum conversion is of considerable practical importance. The experimental evidence relative

to the effects of corticosteroid therapy was discussed in the previous report. The rate of sputum conversion was higher in the prednisolone group up to the end of the fourth month of treatment, the difference being of a highly significant degree at the end of the second month. Attention is also drawn to the fact that of 178 cases admitted to the trial (154 were sputum-positive with tubercle bacilli sensitive to streptomycin, P.A.S., and isoniazid) all but one were culture-negative at the end of six months' treatment. This is in sharp contrast with other series, such as that reported by Weinstein and Koler (1959), in which 16% of patients were stated to be still sputum-positive. There is no indication in their report, however, that the patients' organisms were sensitive initially or that treatment was uniform throughout.

Our experience in respect of sputum conversion differs also from that reported in the preliminary observations of a controlled trial of prednisolone in the treatment of pulmonary tuberculosis carried out in one of the United States Public Health Service Tuberculosis Therapy Trials (1960). The distribution of cases with regard to extent of disease, and the percentage of sputum-positive and cavitated cases, is closely comparable to our own, but the preliminary report states ". . . a nine-week course of steroid . . . resulted in less rapid reversal of infectiousness" (than a five-week course or a placebo). It is not possible from a study of the preliminary report to assess the precise reason for this, but the time over which the trend of reversal of infectiousness in the nine-week-steroid-therapy series becomes unfavourable is also the period during which drug resistance is likely to occur, and one of the regimes of chemotherapy used—streptomycin plus pyrazinamide—is known to give rise to a significant number of drug-resistant cases, as shown in a previous study (United States Public Health Service, 1959). As provision was made in the protocol for the physician to change the assigned regimes, this might also be partly responsible. The strictness of the protocol in our study in regard to uniformity of drug treatment, the use of a combination of drugs known to be highly effective, and the avoidance of surgical treatment in the first six months is emphasized.

In the present trial, prednisolone was responsible for an enhanced rate of improvement in certain respects. These advantages must be balanced against the occurrence of any side-effects which were observed. Important side-effects were noted in two cases (2.3%). One patient developed glycosuria and was shown to have a diabetic curve, and one patient developed a diastolic pressure of 140 mm., prednisolone accordingly being stopped in the sixth week of treatment. No permanent ill effect occurred in either instance. Of the less important side-effects, mooning of the face—sometimes of substantial proportions—was observed in 21% of patients and transient elevation of the diastolic pressure in 13%. Transient glycosuria was reported in 7% of cases.

Corticosteroid therapy is fraught with danger if adequate chemotherapy is not given concurrently, as is made abundantly clear by Des Autels *et al.* (1956). However, in this series of 87 patients in whom every precaution was taken to ensure adequate chemotherapy, no deleterious effect was observed in those treated with prednisolone so far as worsening of the tuberculous disease was concerned, though transient radiographic deterioration—the so-called "rebound" phenomenon—was observed in 11% of patients between the third and fourth months of treatment—that is, on cessation of prednisolone therapy. It is also of interest that prednisolone therapy did not always prevent the occurrence of hypersensitivity reactions to chemotherapy either during treatment or subsequently.

The results of this investigation confirm that prednisolone therapy does not adversely affect the course of pulmonary tuberculosis provided that adequate chemotherapy is given concurrently. Furthermore, prednisolone therapy leads to a rapid abatement of symptoms and consequently may be of considerable value in the seriously ill patient. Sputum conversion is hastened to a statistically significant degree up to the end of the second month. Though the rate of cavity closure is not significantly accelerated, general radiographic improvement is hastened throughout the 12-month period of observation, and significantly so up to the end of the fourth month. Major side-effects were observed in only two cases, but significant mooning of the face occurred in one-fifth of the patients. These results indicate that if the condition of the patient warrants it, prednisolone may be given with reasonable safety in cases of active pulmonary tuberculosis provided the usual strict precautions are observed. It is possible that similar results might have been obtained with a lower dosage of prednisolone and some of the unpleasant side-effects of therapy thereby avoided.

Unfortunately the investigation did not include a study of the effects of prednisolone on pulmonary function. Such investigation might have had important practical implications. If, for example, patients treated with prednisolone *plus* antituberculous chemotherapy were shown at the end of treatment to have significantly better pulmonary function than those treated with antituberculous chemotherapy alone, this would be a formidable argument in favour of treating all cases of extensive pulmonary tuberculosis with corticosteroids.

Summary

The results of treatment in a controlled trial are reported in which 91 patients were treated with chemotherapy alone and 87 with identical chemotherapy plus prednisolone in a dosage of 20 mg. daily for three months. The observation period in all cases was 12 months.

In the prednisolone group clinical improvement was hastened, especially in those acutely ill, and the fall in the erythrocyte sedimentation rate was more rapid.

Although the rate of cavity closure was not increased, general radiographic improvement was more rapid throughout the 12-month period in the prednisolone group, the difference between the two groups being statistically significant in the first four months.

Sputum conversion was hastened in the prednisolone group to a statistically significant degree up to the end of the second month, but by the end of six months no difference was observed, all but one of the 178 cases being sputum-negative on culture.

No permanent deleterious effect was observed in the prednisolone-treated patients, though a temporary "rebound" phenomenon was observed radiographically on ceasing prednisolone therapy in 11% of cases.

Major side-effects were observed in only two of the patients treated with prednisolone.

The need for a study which includes the recording of respiratory function is emphasized.

The Research Committee of the Tuberculosis Society of Scotland wishes to express its gratitude to the physicians, bacteriologists, and nursing staffs of the hospitals concerned for the excellence of their co-operation. The committee is especially indebted to Dr. Douglas Kay, who co-ordinated the trial, and to Mrs. Joan Valentine for very considerable secretarial and statistical assistance. Thanks are also due to Miss Laureen Jackson, Miss Joyce Thornton, Miss Patricia McGuiness, and Miss Maureen Urquhart for secretarial assistance. The Royal Victoria Hospital Tuberculosis Trust gave generous financial aid. The large amount of deltacortril used in this investigation was generously donated by Pfizer Ltd. through the courtesy of Dr. R. Brunton.

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AWARENESS OF FAMILY AND CONTACT HISTORY OF TUBERCULOSIS IN GENERALIZED SARCOIDOSIS

BY

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Sarcoidosis can only be defined at the histological level as the picture of a granuloma containing non-caseating tubercle follicles. Although this is now well known to occur as a local response to a variety of toxic agents and diseases, there is a striking absence of satisfactory evidence that any of these is responsible for the generalized disorder, which is recognized as an entity by its distinctive clinical pattern and course. In spite of this, Jonathan Hutchinson's (1898) original suggestion, that lupus pernio might be tuberculous in origin, has persisted in a belief that generalized sarcoidosis may be a curiously modified form of infection with *Mycobacterium tuberculosis*. The arguments for and against this hypothesis have been reviewed repeatedly in the literature (Pinner, 1938; Hoyle, 1947; Siltzbach, 1958) without result because of the lack of any consistent bacteriological proof. Scadding (1960), in reviewing 230 patients with generalized sarcoidosis, has recorded an interchange between tuberculosis and sarcoidosis in a few individual patients with regard to the disease process, the recovery of bacilli, the immune response, and the effects of appropriate therapy.

It may well be that this type of sarcoidosis is one of an increasing number of disease processes that are being recognized, the basis of which is possibly part infectious and part immune, and which do not fulfil Koch's postulates.

One aspect that may throw some further light on the problem is the incidence of family tuberculosis and of contact with this disease among patients with sarcoidosis. Baas and Vader (1957) have reported contacts with human or bovine tuberculosis surrounding one in three of 128 patients with sarcoidosis—a finding, so far, not implemented in this country. It is the purpose of this investigation to compare and contrast the family and contact history of tuberculosis in a group of patients with sarcoidosis and those of patients with pulmonary tuberculosis on the one hand and with bronchial asthma or bronchitis on the other.

Methods of the Survey

Three series of patients were assembled. The first consisted of 315 patients with pulmonary tuberculosis between the ages of 15 and 55 seen consecutively at the Brompton Hospital between 1950 and 1958 by two physicians. For all these patients a standard form was used and details of family history and contact were taken as part of their history on first admission. These were abstracted from the notes, together with a record of the sputum state during investigation, and the time from contact to the onset of clinical symptoms was noted. Of the 315 reviewed, 80% had *M. tuberculosis* in their sputum.

The second series consisted of 210 patients with sarcoidosis, seen mainly by one physician at King's College Hospital and the Brompton Hospital from 1940 to 1959. The details were taken from the clinical notes, which included the family and contact history of tuberculosis as a routine part of the history. Six patients were questioned where such a record was not noted initially. A note was also made of histological proof, positive in 60% of the 210 patients and of the type of disease. Many without biopsy proof have been followed for several years and have run the same course as the others.

The third series consisted of 214 consecutive patients with asthma and/or bronchitis selected only with regard to age and attending during 1957–9. One group was attending a special clinic at King's College Hospital, where their family and contact histories were taken by those in charge. A second and smaller group was included from the Brompton Hospital to supplement these, using the histories recorded in the admission notes on standard forms. This latter group was used to see if there was a higher incidence of history of contact in asthmatic patients attending a chest hospital with special interest in pulmonary tuberculosis. No evidence of this was found.

It is hoped that the data collected in this way avoid some of the difficulties where interrogation is done by one person who is aware of the issues in question. Fairbairn *et al.* (1959) reported the results of a survey from a questionary by trained doctors and health visitors and showed how the data can vary according to the interpretation and persistence of the questioner. It is hoped that, among the twenty or so doctors covering the period and clinics involved in this survey, the enthusiastic over-reporters will have been matched by those with opposite qualities.

Definitions

The age of each patient was recorded as that when the history was first taken, in order to avoid errors in estimating the duration of the disease. Occupation was noted for all males and single females and classified according to the Index of Occupations collected by the Registrar-General in the census of 1951.